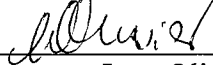


I hereby certify that this correspondence is being filed via  
EFS-Web with the United States Patent and Trademark Office  
on November 1, 2007

PATENT  
Attorney Docket No.: 023070-125630US  
Client Ref. No.: SF 2002-071-2

TOWNSEND and TOWNSEND and CREW LLP

By:   
Lata Olivier

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

HE et al.

Application No.: 10/678,639

Filed: October 3, 2003

For: METHODS FOR TREATING  
CANCER BY INHIBITING WNT  
SIGNALING

Customer No.: 20350

Confirmation No. 7591

Examiner: BRISTOL, Lynn Anne

Technology Center/Art Unit: 1643

**DECLARATION UNDER CFR § 1.131**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

We, Biao HE, Liang YOU, Zhidong XU, and David M. JABLONS, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, hereby declare and state as follows:

1. All statements herein made of our personal knowledge are true and statements made on information or belief are believed to be true. **Exhibits 1-11**, attached hereto, are incorporated herein by reference.

2. We are fully aware of the contents of U.S. patent application Ser. No. 10/678,639 ("639 Application") and its priority provisional application Nos. 60/491,350 ("350 Application"), filed on July 31, 2003 and 60/509,037 ("037 Application"), filed on October 4, 2002.
3. We are co-inventors of the invention disclosed in the '639, '350, and '037 Applications and of the invention claimed in the elected and pending claims 31, 32, 34, 36, and 37.
4. The claimed invention relates, *inter alia*, to a method of inhibiting the growth of a cancer cell that overexpresses a dishevelled-3 (Dvl-3) protein comprising contacting the cancer cell with an agent that inhibits Dvl-3 expression thereby inhibiting the growth of the cancer cell.
5. We have read and we are familiar with the Office Action mailed May 1, 2007. We understand that in the Office Action mailed May 1, 2007, the Examiner has rejected claims 31, 32, 34, and 37 under 35 U.S.C. § 102(e) as allegedly being anticipated by Alsobrook *et al.* (U.S. 2003/0229016, based on U.S. application Ser. No. 10/307,928 ("928 Application"), filed December 2, 2002; "Alsobrook"). According to the Examiner, Alsobrook teaches methods for treating a cancer cell such as a lung cancer cell or a breast cancer cell using an siRNA which inhibits expression of a splice variant of a dishevelled-3-like protein.
6. At the time we first conceived of this invention, we were employed by the Assignee of the '639, '350, and '037 Applications, The Regents Of The University Of California. All the activities described in this declaration took place in the United States.
7. Prior to December 2, 2002, we discovered that Dvl-3 was overexpressed in cancer cells. We showed this by overexpression of the Dvl-3 mRNA and overexpression of Dvl-3 protein in cancer cells.

8. Attached to this Declaration is **Exhibit 1**. **Exhibit 1** includes a page of a laboratory notebook shared by Dr. You and his part-time technician, Keeling Zang, in which they recorded part of their work on the "dishevelled" project. This page of the notebook was written prior to December 2, 2002. The dates have been redacted. Page 1 of **Exhibit 1** shows the experimental details of performing a microarray gene expression (Atlas Cancer Array) and concludes with "good result. worked." Page 2 of **Exhibit 1**, entitled "Identification of Dvl-3-Overexpression Using Microarray Gene Expression (Atlas Cancer Array)" shows Dvl-3 overexpression indicated by spots marked "9." The result thereof identifies Dvl-3 mRNA as one of the genes overexpressed in a tumor tissue when compared to normal tissue. The result shown on page 2 in **Exhibit 1** was obtained prior to December 2, 2002.
9. Attached to this Declaration is **Exhibit 2**. **Exhibit 2** is a page of a laboratory notebook in which Dr. You and his part-time technician, Keeling Zang, recorded part of their work on the "dishevelled" project. This page of the notebook was written prior to December 2, 2002. The dates have been redacted.
10. Page 1 of **Exhibit 2** shows an experimental protocol for determining expression levels of a Dvl-3 proteins in lung tissue samples by Western blot analysis. Tissue samples "10890280 NT" and "0890280 TT" represent lung cells from normal tissue ("NT") and tumor tissue ("TT"), respectively. We used anti-Dvl-3 antibodies ("Primary Ab mouse DVL3 1:400") to detect the Dvl-3 protein in these lung cells. The Western blot result shown on page 2 of **Exhibit 2** demonstrated overexpression of Dvl-3 protein in lung tumor cells (lane marked "0280TT") compared to normal lung tissue (lane marked "0280 NT"). The result shown in **Exhibit 2** was obtained prior to December 2, 2002.
11. Page 1 of **Exhibit 3** shows an experimental protocol for determining expression levels of a Dvl-3 proteins in mesothelioma samples (identified by numbers "10899111," "10891021," "10799111," and "10899120") by Western blot analysis. Mesothelioma samples were from normal tissue ("NT") and tumor tissue ("TT"), respectively. We used

anti-Dvl-3 antibodies ("Primary Ab mouse DVL3 1:400") to detect the Dvl-3 protein in these mesothelioma cells. The Western blot result shown on page 3 of **Exhibit 3** demonstrated overexpression of Dvl-3 protein in 3 out of 4 mesothelioma tumor cells (lanes marked "TT") compared to normal cells (lane marked "NT"). The result shown in **Exhibit 3** was obtained prior to December 2, 2002. Further, Figure 9 of the '037 Application, filed October 4, 2002 shows overexpression of Dvl-3 protein in cancer cells, specifically in several mesothelioma cell lines when compared to normal mesothelioma cells.

12. In addition, prior to December 2, 2002, we determined that some breast cancer cells also overexpressed Dvl-3 when compared to normal epithelial cells.
13. Prior to December 2, 2002 we had discussions as to how to inhibit expression of Dvl proteins, more specifically, a Dvl-3 protein. In particular we proposed inhibiting expression of the Dvl-3 protein using RNA interference (RNAi), more specifically using small interfering RNA (siRNA).
14. Prior to December 2, 2002, we designed and ordered small interfering RNAs (siRNAs) for inhibiting Dvl-3 expression in cancer cells overexpressing a Dvl-3 protein.
15. Prior to December 2, 2002, Kazutsugu Uematsu, who was a post-doctoral fellow working in our laboratory at this time under our supervision, ordered Dvl-3 siRNAs from Ambion, Inc. Austin, TX.
16. **Exhibit 4** shows the receipt of the Dvl-3 siRNAs ordered from Ambion, Inc., Austin, TX. All dates on **Exhibit 4** have been redacted. The order date for the Dvl-3 siRNAs was prior to December 2, 2002.
17. **Exhibit 4** shows (i) the target sequence name, "dv13," which should read "dvl3", (ii) the target sequence (5'-AACAAGATCACCTTCTCCGAG-3'), (iii) the sense sequence (5'-

CAAGAUCACCUUCUCCGAGtt-3' having "tt" added to its 3' end) and (iv) the antisense sequence of the target sequence (5'-CUCGGAGAAGGUGAUCUUGtt-3').

18. **Exhibit 5** shows a human Dvl-3 protein and nucleotide sequence obtained from GenBank accession No. NM\_004423.
19. **Exhibit 6** shows the result of a sequence alignment of the target sequence (5'-AACAAAGATCACCTTCTCCGAG-3') shown in **Exhibit 4** with the Dvl-3 nucleotide sequence of NM\_00423 using BLASTN. This result demonstrates that the target sequence (5'-AACAAAGATCACCTTCTCCGAG-3') and the corresponding antisense sequence of the target sequence (5'-CUCGGAGAAGGUGAUCUUGtt-3') as designed and ordered are found within the Dvl-3 nucleotide sequence.
20. **Exhibit 7** shows the result of a sequence alignment of the sense sequence (5'-CAAGAUCACCUUCUCCGAG-3'; missing the "tt" at the 3' end) with the Dvl-3 nucleotide sequence of NM\_00423 using BLASTN. This result demonstrates that the sense sequence as designed and ordered is found within the Dvl-3 nucleotide sequence.
21. **Exhibits 1-7** are evidence of our conception of the invention, which was complete prior to December 2, 2002, the filing date of Alsobrook's '928 Application.
22. After conceiving of the invention, we worked diligently on the invention during the period of just prior to December 2, 2002, until our invention was actually reduced to practice and constructively reduced to practice with the filing of our '350 Application on July 31, 2003. **Exhibits 8-11** are provided as evidence of diligence and continuous activity relating to the invention. All dates on **Exhibits 8-11** have been redacted.
23. **Exhibit 8** is a page from Kazutsugu Uematsu's laboratory notebook. **Exhibit 8** shows a laboratory procedure to transfect Dvl-3 siRNA into cancer cells to inhibit the growth of the cancer cells, specifically lung cancer cell lines H460 and H1703 and osteosarcoma

cancer cell line Saos-2. We have shown that these cancer cells overexpress the Dvl-3 protein.

24. **Exhibit 9** is a print-out from our laboratory records showing that Dvl-3 siRNA inhibited the growth of the lung cancer cell line H1703, while a control siRNA had no significant effect.
25. **Exhibit 10** is a print-out from our laboratory records showing that Dvl-3 siRNA inhibited the growth of cancer cells, in particular the growth of lung cancer cells H460 and H1703 and the growth of the mesothelioma cell lines H513 and REN, while control siRNA had no such effect on these cancer cell lines.
26. **Exhibit 11** shows a Western blot analysis demonstrating that transfection of the Dvl-3 siRNA into the lung cancer cell line H1703 not only inhibited the growth of this cell line (see above), but also inhibited the expression of the Dvl-3 protein, while a control siRNA had no such effect.
27. We respectfully submit that the facts provided in this Rule 131 Declaration are sufficient to evidence that we completed conception of the invention as claimed prior to December 2, 2002, and that we worked diligently from just prior to December 2, 2002 until constructive reduction to practice on July 31, 2003.

Dated: 10-1-07

Biao He

Biao HE

Dated: 10/1/07

Liang You

Liang YOU

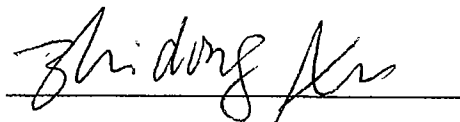
Appl. No. 10/678,639

Rule 131 Declaration

Submitted in Response to Office Action of May 1, 2007

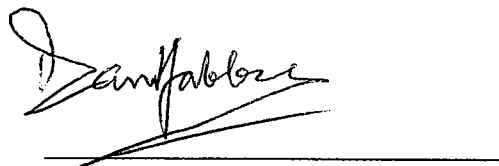
PATENT

Dated: 9/30/07



Zhidong XU

Dated: 10/1/07



David M. JABLONS

61147062 v1

REDACTED

cDNA expression array  
RNA samples meso # 10799 III  
#2 NP #3 M&S  
3  $\mu$ l RNA for each sample

REDACTED

RNA

use column to purify the labeled cDNA from  
unincorporated 32P nucleotides keep the probe at  
-20°C each probe volume is 70  $\mu$ l.

REDACTED

① add 130  $\mu$ l dms to each probe tube  
22  $\mu$ l 10X denaturing solution

68°C 20'

② warm up 10ml express Hyb + 100  $\mu$ l 10mg/l  
salmon sperm DNA (100°C 5' first)

③ 2x 2B, 4B membrane are placed in 80-90°C  
0.5% SDS for 5'

REDACTED

Wash membranes

Solution #1	20'	68°C	x 4
" #2	20'	68°C	x 1
2X SSC	5'	room temp.	

REDACTED

good result worked.

EXHIBIT

1



# Identification of Dvl-3 Overexpression Using Microarray Gene Expression (Atlas Cancer Array)

**NORMAL**

**TUMOR**



cDNA Array Analysis. Representative cDNA spots (each shown in duplicate on the each membrane) that show differences are: 1, p21WAF/CIP1; 2, PCNA; 3, GRB2; 4, DAPK1; 5, SFRP2; 6, RhoA; 7, c-fos; 8, c-met; 9, DVL3; 10, IGFBP2; 11, EGR-1; 12, IL-6; 13, IRF-1.

REDACTED

Prepare protein extract from the lung tissues samples.

10890280 TT  
10890280 NT  
10997021 Mero

use 15ml protein extract buffer for each sample

REDACTED

Measure protein concentration

7021 Mero 0.750 0.7 (5ul) <sup>10</sup> ~~5~~  $\mu\text{g}/\text{ul}$   
0280 TT 0.750 0.5 (10ul) 2.8  $\mu\text{g}/\text{ul}$   
0280 NT 0.94 (10ul) 8  $\mu\text{g}/\text{ul}$

Run on 10% protein gel

	9111 NP	9111 M	0280 NT	0280 TT	7021 M	91201 5000 N
Ladder	21ul	5.1ul	6.25ul	13ul	7ul	10ul 20ul
( <del>7021</del> )	15ug	15ug	50ug	50ug	30ug	15ug 15ug

transfer ON

REDACTED

primary Ab mouse DVL 3 1:400

2<sup>nd</sup> Ab  $\alpha$ -mouse 1:2000

EXHIBIT

2

REDACTED

Western Blot

ladder

020NT

020TT

020M

020M

020M

ladder



DWL 3

REDACTED

Gel 1. from tissue

#	H <sub>2</sub> O	Protein 50µg	3x loading buffer
10899111 AT	7.5µl	5.5µl	7µl
10899111 TT	6.5µl	12.5µl	7
10891021 NT	8.5µl	4.5µl	7
10891021 TT	7.5µl	5.4µl	7
10799111 NT	6.4µl	6.6µl	7
10799111 TT	6.4µl	6.6µl	7
10899120 NT	6.7	6.3	7
10899120 TT	5.9	7.1	7

Gel 2 cells

#	H <sub>2</sub> O	Protein 50µg	3x loading buffer
tissue 10895101 NT	8µl	5µl	7
cell 10799111	5µl	8µl	7
✓ MS-1	4.7	8.3	7
✓ 211 H	6.4	6.6	7
✓ H 2052	2.1	10.9	7
✓ 1089 2120	2.4	7.6	7
✓ Met 5A	7.9	5.1	7
✓ H 573	5.2	7.8	7

EXHIBIT

3

REDACTED

Primary Ab. ~~Ab~~-mouse DVL-3 1:400 O/N

REDACTED

Second Ab  $\alpha$  mouse HRP labelled Ab 1:2000  
5:20 pm - 5:20 pm

REDACTED

- Run a 10% protein gel. say protein for sample.  
marker 1089911  $\rightarrow$  10891021 1079911 10899120 108  
AT, TT NT, TT NT, TT NT, TT

- Transfer 4°C, O/N, 40 volts

REDACTED

Wash w/ TBS-T, 2nd Ab  
develop film

REDACTED

Prepare	Samples	for frozen section	(Tissues)
10795121	NL, LC	10895170	NL, LC
10897180	NL, LC	10791270	NL, LC
10898111	NL, LC	10893061	NL, LC
10890311	NL, LC	10898060	NL, LC
10891601	NL, LC	10892180	NL, LC
20891150	NL, LC		

REDACTED

Western

1	Marker
2	1089911 AT
3	1089911 TT
4	1089911 BT
5	1089911 T
6	1089911 NT
7	1089911 TT
8	1089911 BT
9	1089911 T
10	1089911 NT

DVL3

CustomerName  
Kazutsugu Uematsu

PO Number  
1B017A2111RESEA

Institution  
UCSF Cancer Center

OrderDate

**REDACTED**

SEE SEQUENCE ID ON BACK OF BOX

Target Sequence Name  
dv13

SiRNA Kit Lot #  
072R03A

**Target Sequence**

5' AACAGATCACCTTCTCCGAG 3'

**Sense Sequence**

5' CAAGAUCACCUUCUCCGAGtt 3'

Seq. Lot #  
026178

Length	Molecular Weight	%GC	Ext. Coef.
21	6589.2	48	198400 L/(mole·cm)
OD260	Micrograms	Nanomoles	
5.16	171.3636	26.0064	

\*Using Nearest Neighbor equation

1 OD(260)=  
33.21 Micrograms  
5.04 nanomoles

100µM solution DW 260µl

**Antisense Sequence**

5' CUCGGAGAAGGUGAUCUUGtt 3'

Seq Lot #  
026179

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OD260	Micrograms	Nanomoles	
4.89	158.3382	23.5209	

\*Using Nearest Neighbor equation

1 OD(260)=  
32.38 Micrograms  
4.81 nanomoles

100µM solution DW 235µl

Scale  
0.20 micromolar

Purification  
PAGE

5' Modifications  
N/A

Internal Modifications  
N/A

3' Modifications  
N/A

QC

Date

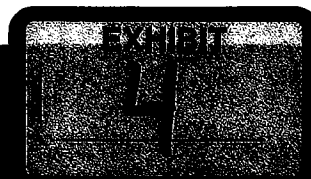
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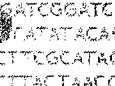
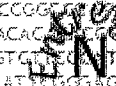


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0699

**REDACTED**




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Display  Show   Hide: ☐ sequence ☐ all but gene, CDS and mRNA

Range: from  to  ☐ Reverse complemented strand Features: ☐ SNP ☒ STS ☒

☐ 1: NM\_004423. Reports Homo sapiens dish...[gi:41406096]

Order cDNA clone,  
Links

[Comment](#) [Features](#) [Sequence](#)

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 ACCESSION NM\_004423  
 VERSION NM\_004423.3 GI:41406096  
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 ORGANISM Homo sapiens  
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 Catarrhini; Hominidae; Homo.

REFERENCE 1 (bases 1 to 5062)  
 AUTHORS Chan,D.W., Chan,C.Y., Yam,J.W., Ching,Y.P. and Ng,I.O.  
 TITLE Prickle-1 negatively regulates Wnt/beta-catenin pathway by promoting Dishevelled ubiquitination/degradation in liver cancer  
 JOURNAL Gastroenterology 131 (4), 1218-1227 (2006)  
 PUBMED 17030191  
 REMARK GeneRIF: The facilitation of Prickle-1 on Dvl3 degradation and the suppression of beta-catenin activity and cell growth suggest that Prickle-1 is a negative regulator of the Wnt/beta-catenin signaling pathway

REFERENCE 2 (bases 1 to 5062)  
 AUTHORS Song,D.H., Sussman,D.J. and Seldin,D.C.  
 TITLE Endogenous protein kinase CK2 participates in Wnt signaling in mammary epithelial cells  
 JOURNAL J. Biol. Chem. 275 (31), 23790-23797 (2000)  
 PUBMED 10806215

REFERENCE 3 (bases 1 to 5062)  
 AUTHORS Kishida,S., Yamamoto,H., Hino,S., Ikeda,S., Kishida,M. and Kikuchi,A.  
 TITLE DIX domains of Dvl and axin are necessary for protein interactions and their ability to regulate beta-catenin stability  
 JOURNAL Mol. Cell. Biol. 19 (6), 4414-4422 (1999)  
 PUBMED 10330181

REFERENCE 4 (bases 1 to 5062)  
 AUTHORS Bui,T.D., Beier,D.R., Jonssen,M., Smith,K., Dorrington,S.M., Kaklamani,L., Kearney,L., Regan,R., Sussman,D.J. and Harris,A.L.  
 TITLE cDNA cloning of a human dishevelled DVL-3 gene, mapping to 3q27, and expression in human breast and colon carcinomas  
 JOURNAL Biochem. Biophys. Res. Commun. 239 (2), 510-516 (1997)  
 PUBMED 9344861

REFERENCE 5 (bases 1 to 5062)  
 AUTHORS Semenov,M.V. and Snyder,M.





TITLE Human dishevelled genes constitute a DHR-containing multigene family

JOURNAL Genomics 42 (2), 302-310 (1997)

PUBMED 9192851

REFERENCE 6 (bases 1 to 5062)

AUTHORS Pizzuti,A., Amati,F., Calabrese,G., Mari,A., Colosimo,A., Silani,V., Giardino,L., Ratti,A., Penso,D., Calza,L., Palka,G., Scarlato,G., Novelli,G. and Dallapiccola,B.

TITLE cDNA characterization and chromosomal mapping of two human homologues of the Drosophila dishevelled polarity gene

JOURNAL Hum. Mol. Genet. 5 (7), 953-958 (1996)

PUBMED 8817329

COMMENT REVIEWED, REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from [U75651.1](#) and [D86963.1](#). On Jan 30, 2004 this sequence version replaced [gi:6806886](#).

Summary: This gene is a member of a multi-gene family which shares strong similarity with the Drosophila dishevelled gene, dsh. The Drosophila dishevelled gene encodes a cytoplasmic phosphoprotein that regulates cell proliferation.

COMPLETENESS: complete on the 3' end.

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	2832-3084	D86963.1	2832-3084	
	3085-3152	U75651.1	3336-3403	
	3153-5062	D86963.1	3153-5062	

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    polyA site 2482
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              recorded"
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              /db_xref="UniSTS:11756"
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## ORIGIN

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121 cggggcccga ggccagagcc atgggcgaga ccaagatcat ctaccacttg gatgggcagg
181 agacgccgta ccttgtgaag ctgcccctgc ccgccgagcg cgtcaccttg gcggacttta
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481 ccccatcctt ccacctcat gctgggtggg gcagccagga gaacctggac aatgacacag
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```

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2401 gaactaaatc caggtgcgct aactgctcgc aggtgtgctg gaggtgggg tgacactacc
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4561 gtcattcatc ctgatgtcct caattgctgc tgatatgctg gtgattccca aatacatagc
4621 tccaaccccc aacttcccc agactttaga tctgtattgg tattacctac tggacatctc
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4681 tatggacagt tccgtataga ctcaactcat ctgcccacc aagtatgttc ctctgaatt
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4981 tttaacctct ctgagcctca gttccctcgt atgtaaaatg atgataataa tacctacctc
5041 acagggttgt tgtgaggatt ta
```

//

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Aug 28 2007 16:53:42



## Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

### BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.17 [Aug-26-2007]

Match:  Mismatch:  gap open:  gap extension:   
x\_dropoff:  expect:  wordsize:  Filter ☒ View option   
Masking character option ☒ X for protein, n for nucleotide Masking color option   
☐ Show CDS translation

**Sequence 1:** lcl|1

Length = 21 (1 .. 21)

**Sequence 2:** lcl|65536

Length = 5062 (1 .. 5062)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 41.1 bits (21), Expect = 0.019  
Identities = 21/21 (100%), Gaps = 0/21 (0%)  
Strand=Plus/Plus

```
Query 1      AACAAAGATCACCTTCTCCGAG  21
            |||
Sbjct 1584   AACAAAGATCACCTTCTCCGAG  1604
```

CPU time: 0.09 user secs. 0.03 sys. secs 0.12 total secs.





# Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

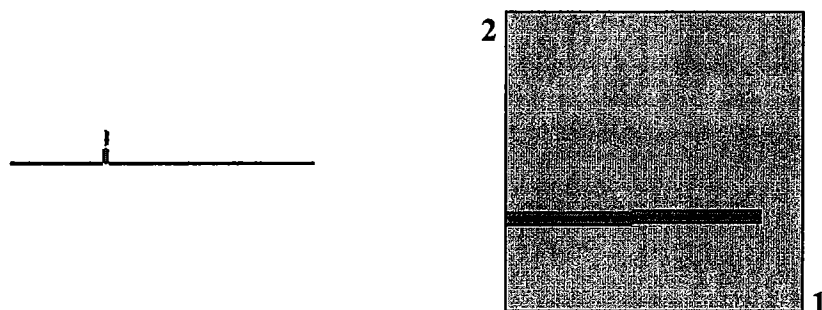
## BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.17 [Aug-26-2007]

Match:  Mismatch:  gap open:  gap extension: x\_dropoff:  expect:  wordsize:  Filter ☒ View option Masking character option ☒ X for protein, n for nucleotide Masking color option ☐ Show CDS translation **Sequence 1:** lcl|1

Length = 21 (1 .. 21)

**Sequence 2:** lcl|65536

Length = 5062 (1 .. 5062)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



Score = 37.2 bits (19), Expect = 0.27  
Identities = 19/19 (100%), Gaps = 0/19 (0%)  
Strand=Plus/Plus

Query 1 CAAGATCACCTTCTCCGAG 19  
|||||  
Sbjct 1586 CAAGATCACCTTCTCCGAG 1604

CPU time: 0.10 user secs. 0.04 sys. secs

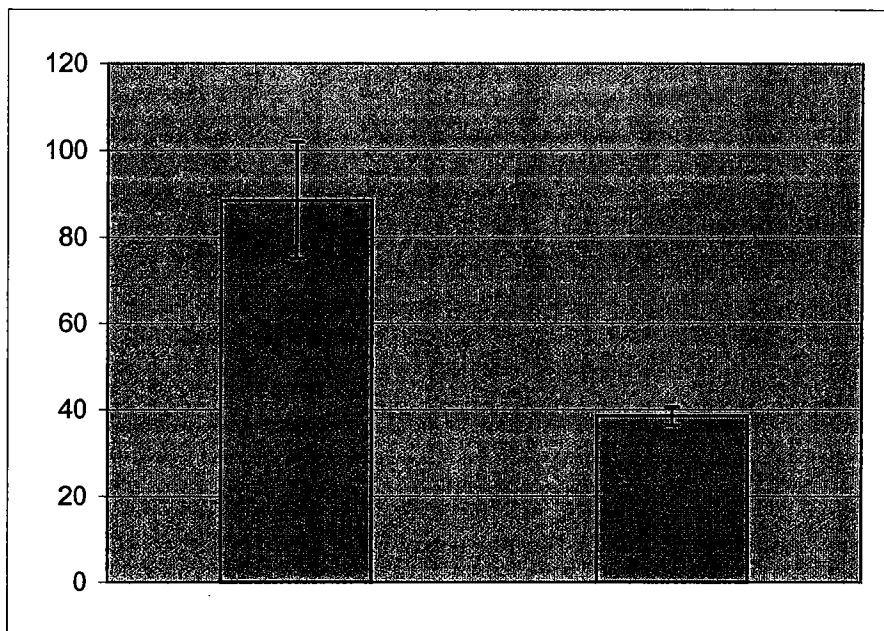
0.14 total secs.







H1703	500/dish	
	controlsiRNA	DvlsiRNA
colony count	79	40
	98	37
ave	88.5	38.5
SD	13.43503	2.12132
TTEST	0.035065	



**REDACTED**

H1703/

hr DvlsiRNA		control		DvlsiRNAa cont ave		DvlsiRNAAd cont dev	
A	B	A	B				
0	2.4	2.4	2.4	2.4	2.4	0	0
72	4.444444	6	18.66667	19.33333	5.222222	19	1.099944 0.471405
96	4.044444	8.222222	24.22222	24.44444	6.133333	24.33333	2.954135 0.157135
120	5.111111	9.333333	31.77778	35.77778	7.222222	33.77778	2.985562 2.828427
144	11.33333	11.55556	54.66667	65.55556	11.44444	60.11111	0.157135 7.699607

P  
A549/

**REDACTED**

hr DvlsiRNA		control		DvlsiRNAa cont ave		DvlsiRNAAd cont dev	
A	B	A	B				
0	0.4	0.4	0.4	0.4	0.4	0	0
50	1.35	2.24	1.83	1.59	1.795	1.71	0.629325 0.169706
74	5.555556	5.333333	3.555556	4	5.444444	3.777778	0.157135 0.31427
98	8.222222	8	10	11.11111	8.111111	10.55556	0.157135 0.785674
124	18	18.66667	14	12.22222	18.33333	13.11111	0.471405 1.257079
180	36.88889	36.22222	14	27.33333	36.55556	20.66667	0.471405 9.42809

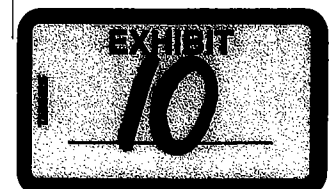
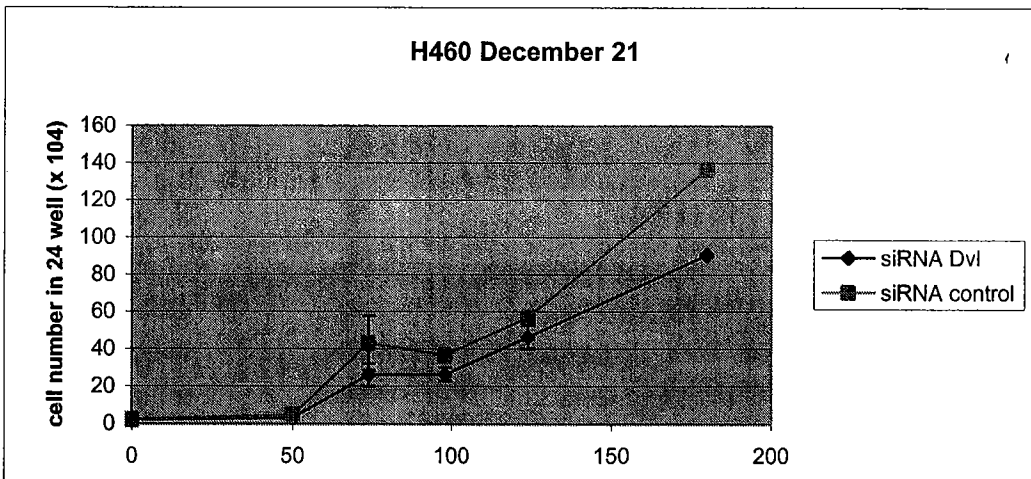
H51301/**REDACTED**

hr DvlsiRNA		control		DvlsiRNAa cont ave		DvlsiRNAAd cont dev	
A	B	A	B				
0	3.555556	3.555556	3.555556	3.555556	3.555556	0	0
48	3.777778	5.111111	3.777778	4.222222	4.444444	4	0.942809 0.31427
109	6	2.444444	4.222222	3.555556	4.222222	3.888889	2.514157 0.471405
144	3.777778	3.111111	7.555556	4.666667	3.444444	6.111111	0.471405 2.042753
192	5.555556	5.555556	9.555556	10.66667	5.555556	10.11111	0 0.785674
216	5.333333	7.333333	13.77778	17.11111	6.333333	15.44444	1.414214 2.357023

**REDACTED**

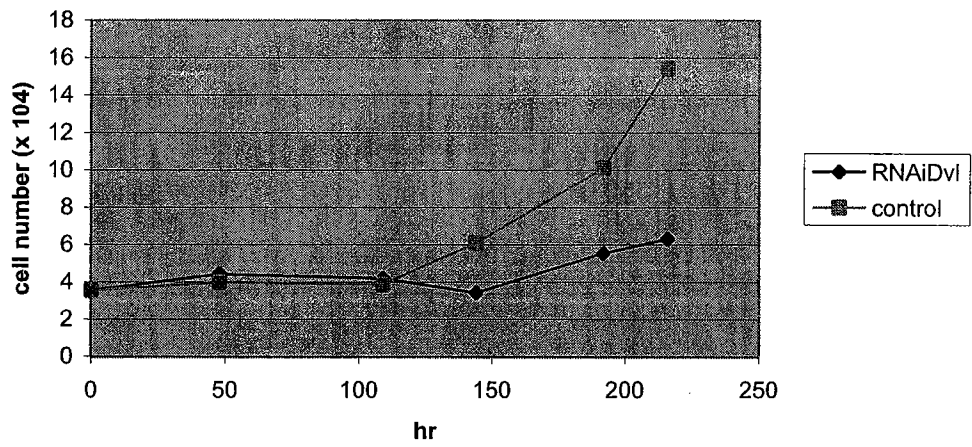
REN

hr DvlsiRNA		control		DvlsiRNAa cont ave		DvlsiRNAAd cont dev	
A	B	A	B				
0	2.666667	2.666667	2.666667	2.666667	2.666667	0	0
48	9.111111	10.44444	11.11111	8	9.777778	9.555556	0.942809 2.199888
72	20.88889	13.77778	16	17.77778	17.33333	16.88889	5.028315 1.257079
96	18.66667	18.22222	27.55556	26.88889	18.44444	27.22222	0.31427 0.471405
120	24.66667	27.11111	29.33333	33.77778	25.88889	31.55556	1.728483 3.142697

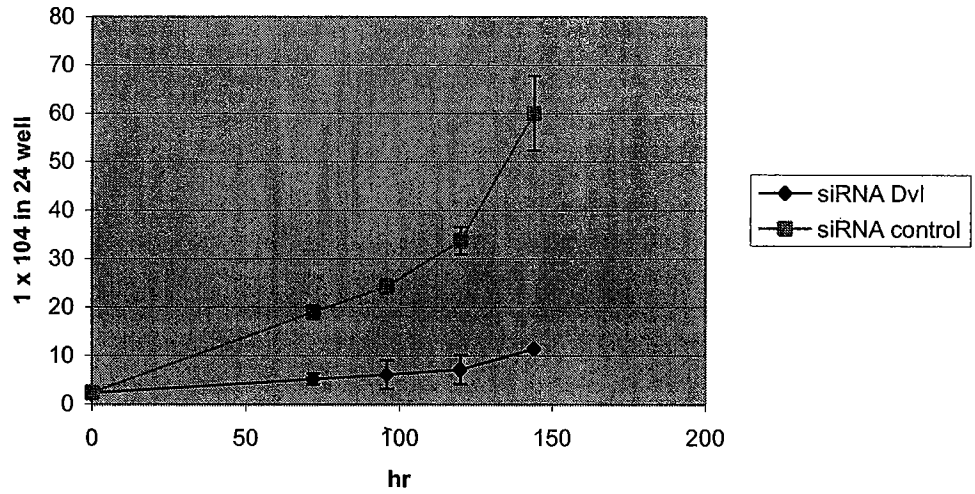


hr

### H513



### H1703



# REDACTED

p

H460

	hr	DvlsiRNA		control		DvlsiRNAa cont ave			DvlsiRNAd
		A	B	A	B				
	0	7.2		7.2	7.2	7.2	7.2	7.2	0
0.003751	72	45		43	47	70.5	44	58.75	1.414214
0.012954	96	51.5		51	66	70	51.25	68	0.353553
0.011781	120	79		72.5	88.5	90	75.75	89.25	4.596194
0.01229	144	110		108	133.5	143	109	138.25	1.414214

# REDACTED

H460/

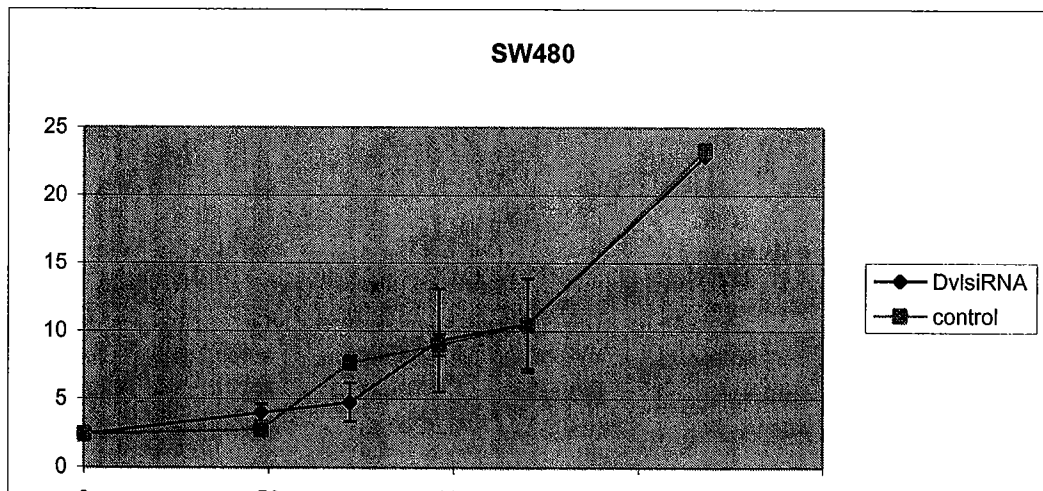
	hr	DvlsiRNA		control		DvlsiRNAa cont ave			DvlsiRNAd
		A	B	A	B				
	0	2.3		2.3	2.3	2.3	2.3	2.3	0
0.870688	50	3.12		3.12	3.87	5.12	3.12	4.495	0
0.021508	74	30.5		22	53.5	33	26.25	43.25	6.010408
0.049745	98	24		29	36	37.5	26.5	36.75	3.535534
0.031494	124	51		42	54.5	59.5	46.5	57	6.363961
0.140284	180	90.5		90.5	136.5	136.5	90.5	136.5	0

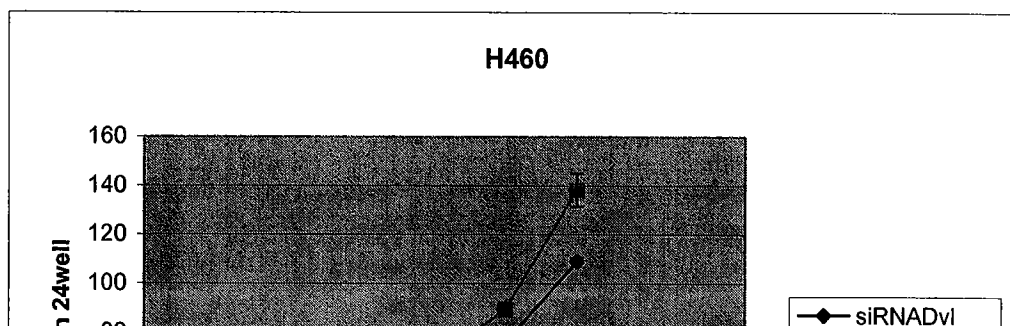
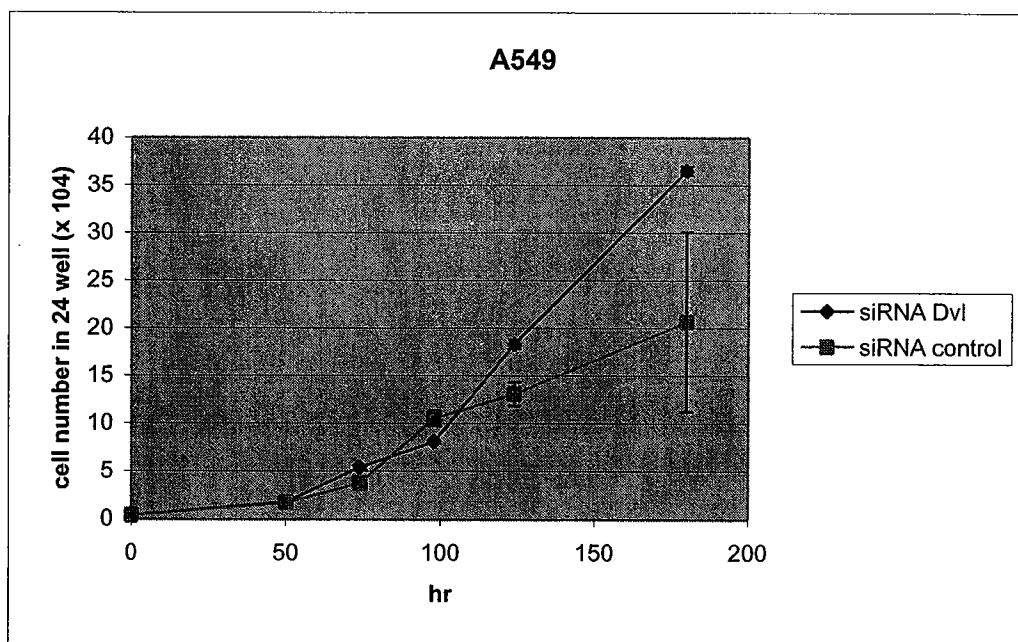
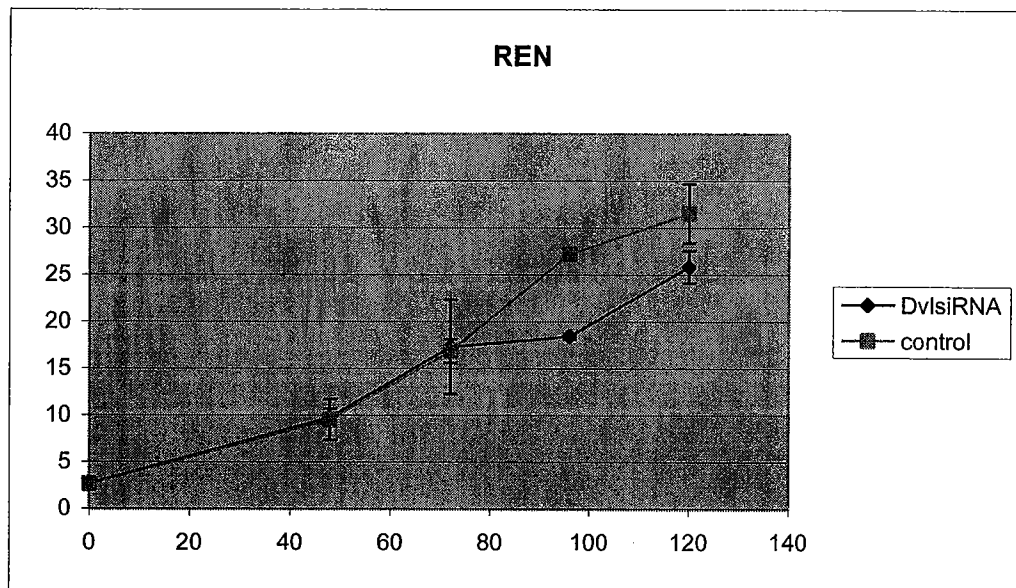
# REDACTED

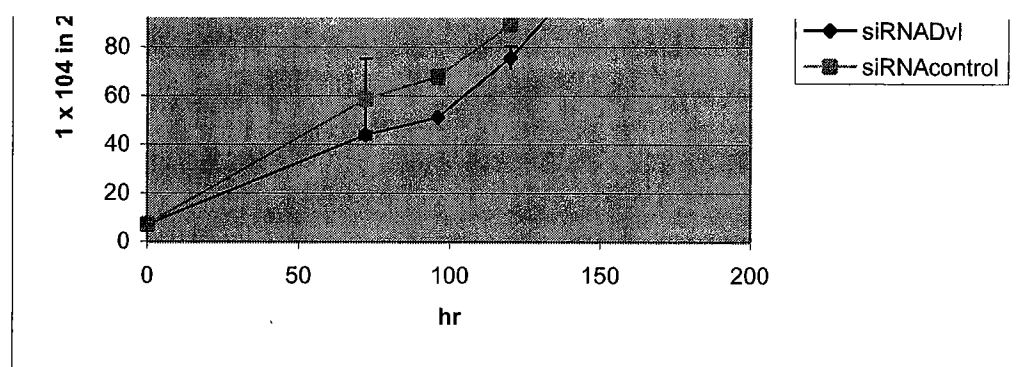
SW480

	hr	DvlsiRNA		control		DvlsiRNAa cont ave			DvlsiRNAd
		A	B	A	B				
	0	2.4		2.4	2.4	2.4	2.4	2.4	0
0.591752	48	3.555556	4.444444	2.444444	3.111111	4	2.777778	0.628539	
0.870781	72	5.777778	3.777778	7.333333	8	4.777778	7.666667	1.414214	
0.213854	96	6.666667	12	9.555556	8.444444	9.333333	9	3.771236	
0.014548	120	12.88889	8.222222	12.88889	8	10.55556	10.44444	3.299832	
0.04262	168	22.88889	22.88889	23.33333	23.33333	22.88889	23.33333	0	

0.90755  
0.914564  
0.002077  
0.155031







cont dev

0  
16.61701  
2.828427  
1.06066  
6.717514

cont dev

0  
0.883883  
14.49569  
1.06066  
3.535534  
0

cont dev

0  
0.471405  
0.471405  
0.785674  
3.456966  
0

REDACTED

H1113

4013

1000000

1000000

1000000

1000000

1000000

1000000

1000000

EXHIBIT

11